Comparison of Etanercept Monotherapy and Combination Therapy with Methotrexate in Psoriatic Arthritis: Results from 2 Clinical Trials

Bernard Combe, Frank Behrens, Neil McHugh, Fiona Brock, Urs Kerkmann, Blerina Kola, and Gaia Gallo

ABSTRACT. ***Objective.*** To evaluate the clinical/functional outcomes associated with etanercept (ETN) monotherapy versus combination therapy in psoriatic arthritis (PsA).

Methods. Data from patients with PsA who received ETN alone (n = 322) or combined with methotrexate (MTX; n = 152) for 24 weeks in 2 placebo-controlled clinical trials were summarized across studies.

Results. Similar proportions of patients in the monotherapy and combination therapy groups achieved the PsA Response Criteria (80% and 83%) and the American College of Rheumatology improvements of 20% (ACR20; both 70%); numerically higher proportions receiving monotherapy achieved ACR50 (55% vs 48%) and ACR70 (35% vs 27%). Little between-group difference was observed in the 28-joint Disease Activity Score with C-reactive protein, the Psoriasis Area and Severity Index, and the Health Assessment Questionnaire–Disability Index improvement.

Conclusion. ETN with and without MTX provided similar benefits in active PsA. (J Rheumatol First Release May 1 2016; doi:10.3899/jrheum.151290)

Key Indexing Terms:
PSORIATIC ARTHRITIS | DISEASE-MODIFYING ANTIRHEUMATIC DRUGS
ETANERCEPT | BIOLOGIC | METHOTREXATE

In patients with chronic inflammatory diseases, antitumor necrosis factor (anti-TNF) agents are often administered in combination with the synthetic disease-modifying antirheumatic drug (DMARD) methotrexate (MTX) to enhance clinical outcomes, reduce the risk of immunogenicity, and improve drug survival[1]. In rheumatoid arthritis (RA), evidence from comparative controlled trials of anti-TNF agents and current treatment guidelines strongly support the use of such combination therapy because it was proven to be more effective than anti-TNF monotherapy[2,3,4,5,6]. Randomized controlled trials in psoriatic arthritis (PsA) have evaluated the efficacy and safety of etanercept (ETN), adalimumab (ADA), and infliximab (IFX) as monotherapy and as add-on therapy to ongoing MTX treatment[7,8,9,10,11,12,13]. However, to date, no study has directly compared outcomes in patients receiving anti-TNF monotherapy or anti-TNF with MTX combination therapy. Current treatment guidelines do not include recommendations on the appropriate use of biologics as monotherapy or combined with MTX[14,15,16].

ETN has been studied in 2 main placebo-controlled trials in PsA[7,9]. In a 12-week, single-center trial[9], patients with active disease despite stable doses of MTX were permitted to continue receiving nonbiologic DMARD and were randomized to ETN 25 mg twice weekly (BIW) subcutaneously, or placebo. At Week 12, 87% and 23% of patients in the ETN and placebo groups, respectively, met the PsA Response Criteria (PsARC). In a larger multicenter study[7], in which background MTX was also allowed but not mandatory, at 12 and 24 weeks, PsARC response was achieved by 72% and 70% of patients receiving ETN 25 mg BIW compared with 31% and 23% of those receiving placebo, respectively. In the Psoriasis Randomized Etanercept Study in Subjects with Psoriatic Arthritis (PRESTA), patients were randomized to receive ETN 50 mg BIW or 50 mg once weekly (QW) subcutaneously for 12 weeks[8]; patients continued treatment with ETN 50 mg QW

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open label for 12 additional weeks, with the option of continuing stable doses of MTX through both study phases. In PRESTA, similar proportions of patients in the BIW and QW groups achieved PsARC response at weeks 12 and 24 (i.e., 77% vs 76%, and 82% and 80%, respectively).

Because the design and patient populations of the latter two 24-week clinical trials were relatively similar, posthoc analyses were conducted using pooled data from the trials to evaluate potential differences in clinical and functional outcomes in patients with PsA who received ETN with and without MTX[7,8].

MATERIALS AND METHODS

Study design and patients. Adult patients (aged ≥ 18 yrs) with active PsA who participated in the selected studies were divided into 2 groups: patients who received ETN 25 mg BIW[7] or 50 mg QW[8] without concomitant MTX were included in the monotherapy group, and patients who received ETN 25 mg BIW[7] or 50 mg QW[8] with concomitant MTX were included in the combination therapy group. The ETN 50 mg BIW group in the PRESTA study[8] was excluded from these analyses. In the combination therapy group, MTX could have been continued at stable dosages of ≤ 25 mg/week[7] or ≤ 20 mg/week[8]. Patients in this group were required to have received ETN plus MTX on at least 1 occasion, but their therapy was not restricted exclusively to this combination for the 24-week study period.

Assessments. Clinical efficacy was measured by comparing the proportions of patients who achieved the PsARC, the American College of Rheumatology (ACR) improvements of 20% (ACR20), 50% (ACR50), and 70% (ACR70), and the Psoriasis Area Severity Index (PASI) improvement of 75% (PASI75) in the ETN monotherapy and combination therapy groups across both studies after 24 weeks of treatment. Assessments of clinical efficacy in joints and skin also included improvement from baseline to Week 24 in the 28-joint Disease Activity Score (DAS28) with C-reactive protein (CRP) and the PASI. Physical function was measured using the Health Assessment Questionnaire-Disability Index (HAQ-DI).

Statistical analysis. Demographic and disease activity characteristics of patients in the monotherapy and combination therapy groups [intention-to-treat (ITT) populations] across both studies at baseline are summarized using descriptive statistics, as are data for categorical and continuous efficacy/functional variables. Percentage response at 24 weeks to the PsARC, ACR20, ACR50, ACR70, and PASI75 were calculated for each treatment arm. Mean response at 24 weeks and the 24-week change from baseline were calculated for the DAS28-CRP, PASI, and HAQ-DI for each treatment arm. Because the treatment comparison was not part of the randomized design of the original studies, no formal hypothesis testing was applied; 95% CI were calculated to assist with the interpretation of the estimated values.

RESULTS

Patients. A total of 322 ITT patients were included in the ETN monotherapy group and 152 ITT patients in the combination therapy group. In the monotherapy group, 56 patients received ETN 25 mg BIW[7] and 266 patients received ETN 50 mg QW[8]. In the combination therapy group, 45 patients received the BIW dosage[7] and 107 patients the QW dosage[8]. The mean weekly MTX dosage was 13.8 mg (SD 4.9) in the combination therapy group.

Baseline demographic and disease characteristics were similar across the groups (Table 1). The mean duration of PsA in patients receiving ETN monotherapy was 8.2 years (SD 7.8) and in those receiving combination therapy, 9.0 years (SD 7.0). The mean duration of psoriasis in patients receiving ETN monotherapy was 18.4 years (SD 12.0), and in those receiving combination therapy, 17.5 years (11.0).

Table 1. Baseline demographic and disease characteristics. Values are mean (SD) unless otherwise specified.

Characteristics	ETN Monotherapy, n = 322	ETN + MTX Combination Therapy, n = 152
Demographics		
Age, yrs	47.0 (11.7)	47.2 (11.0)
Female, n (%)	123 (38.2)	64 (41.8)
White, n (%)	292 (90.7)	135 (88.8)
Disease history		
Duration of PsA, yrs	8.2 (7.8)	9.0 (7.0)
Duration of psoriasis, yrs	18.4 (12.0)	17.5 (11.0)
Joint disease characteristics		
DAS28*	4.7 (1.2), n = 232	4.7 (1.1), n = 123
Distal interphalangeal, n (%)	59 (18.3)	21 (13.8)
Polyarticular arthritis, n (%)	201 (62.4)	104 (68.4)
Arthritis mutilans, n (%)	2 (0.6)	1 (0.7)
Asymmetric peripheral arthritis, n (%)	95 (29.5)	39 (25.7)
AS symptoms, n (%)	21 (6.5)	13 (8.6)
Skin disease characteristics		
PASI*	18.3 (10.2), n = 278	16.1 (9.6), n = 128
BSA affected by psoriasis*, %	28.0 (23.4), n = 302	22.9 (20.0), n = 143
Physical function		
HAQ-DI*	0.9 (0.7), n = 295	1.1 (0.7), n = 141

* Baseline values for these joint/skin disease and physical function assessments were derived from a subset of patients with 24-week data (as noted). ETN: etanercept; MTX: methotrexate; PsA: psoriatic arthritis; DAS28: Disease Activity Score in 28 joints; AS: ankylosing spondylitis; PASI: Psoriasis Area Severity Index; BSA: body surface area; HAQ-DI: Health Assessment Questionnaire–Disability Index.

Clinical/functional outcomes. Clinical efficacy in joints was similar for the monotherapy and combination therapy regimens over 24 weeks based on most outcomes measured. PsARC was achieved by 80.3% (95% CI 75.8–84.8) and 82.6% (76.5–88.8) of patients in the monotherapy and combination therapy groups, respectively, and an ACR20 response in about 70% in both groups (70.5%, 65.2–75.8 and 69.9%, 62.4–77.5; Figure 1). Numerically higher proportions of patients in the monotherapy group achieved ACR50 (54.9%, 49.1–60.6 vs 48.3%, 40.1–56.4) and ACR70 (34.7%, 29.2–40.2 vs 26.6%, 19.3–33.8) responses. Similar mean improvements in the DAS28 (–1.85, –2.03 to –1.68 and –1.84, –2.04 to –1.64) were also observed in these groups from baseline to Week 24 (Figure 2A).

Clinical responses in skin were also comparable. A PASI75 response was achieved by 59.7% (54.0–65.5) and 58.6% (50.1–67.1) of patients receiving monotherapy and combination therapy, respectively (Figure 1). Mean improvements in the PASI (–13.60, –14.73 to –12.47 and –12.18, –13.84 to –10.53) were similar between groups from

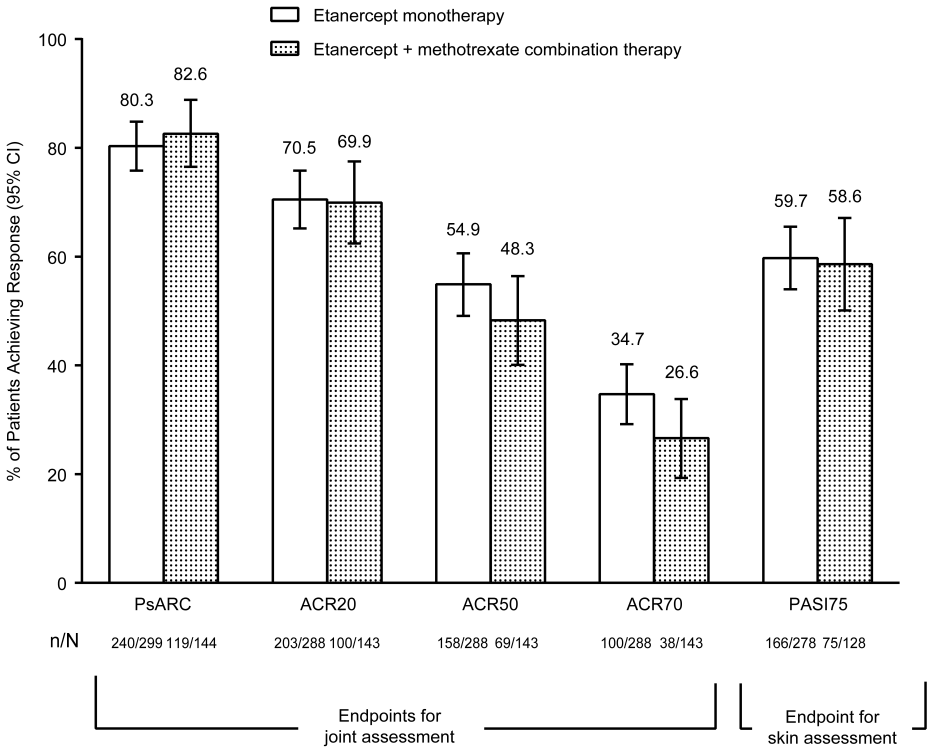

Figure 1. Proportions of patients (95% CI) achieving clinical responses (joint and skin) at Week 24. PsARC: Psoriatic Arthritis Response Criteria; ACR20: American College of Rheumatology improvements of 20%; ACR50: ACR improvements of 50%; ACR70: ACR improvements of 70%; PASI75: Psoriasis Area and Severity Index improvement of 75%.

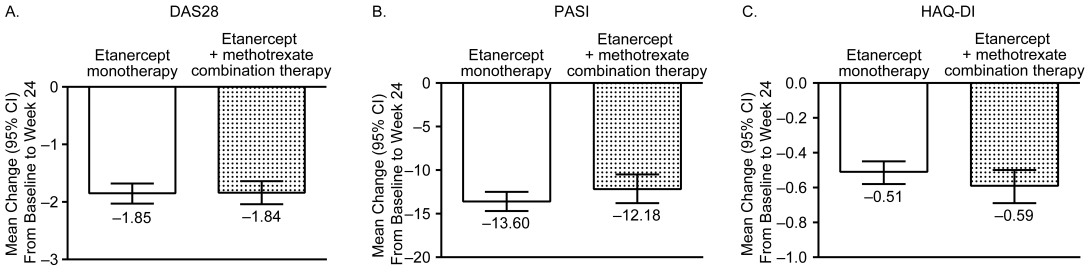

Figure 2. Mean changes (95% CI) from baseline to Week 24. (A) DAS28. (B) PASI. (C) HAQ-DI. DAS28: 28-joint Disease Activity Score; PASI: Psoriasis Area and Severity Index; HAQ-DI: Health Assessment Questionnaire–Disability Index.

baseline to Week 24 (Figure 2B). In addition, minimal difference in improvement in the HAQ-DI (–0.51, –0.58 to –0.45 and –0.59, –0.69 to –0.50) was observed between the groups from baseline to Week 24 (Figure 2C).

DISCUSSION

In these analyses, patients with active PsA who had been treated with ETN with or without MTX achieved similar improvements in clinical and functional outcomes after 24 weeks of treatment. MTX coadministration had minimal effect on the efficacy of ETN in terms of the joints, skin, or physical function in PsA. Our findings are not in agreement with evidence from controlled trials and management guidelines in RA that support the use of biologic therapy in combination with MTX rather than biologic monotherapy because of superior efficacy[2,3,4,5,6], but they are consistent with results of systematic reviews of randomized trials in PsA[17], registries[18,19], and observational studies[20], which reported similar responses to anti-TNF agents administered alone and with MTX in patients with PsA in a real-world setting.

In systematic reviews, anti-TNF agents combined with MTX in PsA were not found to provide greater improvement in clinical symptoms than anti-TNF monotherapy, but combination therapy appeared to be involved in prolonging anti-

TNF therapy continuation and decreasing side effects[17,21]. Patients treated with anti-TNF agents and concomitant MTX in the Southern Swedish Arthritis Treatment Group registry had significantly better drug survival, primarily because of fewer dropouts owing to adverse events, than those treated with anti-TNF monotherapy[18]. In the British Society for Rheumatology Biologics Register and the Norwegian longitudinal observational study on DMARD, concomitant MTX was not associated with an advantage over anti-TNF monotherapy in terms of efficacy. However, drug survival was superior in patients treated with IFX and ADA who received MTX, but not in patients treated with ETN[19,20], suggesting that outcomes may be dependent on the individual biologic assessed. Similarly, in the observational PROVE study, drug survival over 5 years in patients treated with ETN with PsA was not significantly affected by the use of MTX[22]. Drug survival may be influenced by multiple factors, including patient adherence, treatment efficacy, safety and tolerability, and the development of antidrug antibodies. Antidrug antibodies against the anti-TNF monoclonal antibodies IFX and ADA have been shown to substantially reduce response rates, an effect that is diminished by concomitant MTX; in contrast, antibodies against the fusion receptor protein ETN are rarely detected[23]. Although immunogenicity was not analyzed in the aforementioned studies, this factor may explain, at least in part, the different drug survival profiles associated with these agents.

Among the strengths of these analyses are the large number of patients included and the use of randomized controlled studies. However, these studies were not designed or sized to address differences in clinical outcomes between anti-TNF agents used as monotherapy or in combination with MTX, which is a limitation of our analyses. Patients were not randomized to receive anti-TNF monotherapy or combination therapy, introducing potential bias. In addition, our study duration of 24 weeks was not sufficient to identify longterm treatment effects.

MTX administered in combination with the anti-TNF agent ETN in patients with PsA may not provide significantly greater improvement in arthritis or psoriasis symptoms than ETN monotherapy. This finding may be particularly important in patients with intolerance or contraindications to MTX treatment. Further research is warranted to better understand the potential advantages and disadvantages of MTX use with anti-TNF therapy for PsA.

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